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| EXAMINER | |
|---|---|
| BRISTOL, LYNN ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/534,773 | ROBERTSON ET AL. | |
| | Examiner | Art Unit | |
| | LYNN BRISTOL | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8,11,12 and 15-18* is/are pending in the application.

4a) Of the above claim(s) *15 -18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/23/08 has been entered.

2. Claims 1-8, 11, 12 and 15-18 are all the pending claims for this application.

3. Claims 15 -18 are withdrawn from examination.

4. Claim 1 is amended in the Response of 6/23/08.

5. Claims 1-8, 11 and 12 are all the pending claims under examination.

### ***Withdrawal of Rejections***

### *Claim Rejections - 35 USC § 112, second paragraph*

6. The rejection of Claims 1-8, 11 and 12 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps is withdrawn.

Applicants did not address this rejection in their Response of 7/5/07. Applicants have now addressed the rejection in the Response of 6/23/08 by explaining the meaning of the phrase “immunoassay reagent” as described in the specification on p. 10 at lines 15-19 and 24-29.

7. The rejection of Claims 1-8, 11 and 12 for the recitation "one or more tumor marker protein prepared from a bodily fluid, *derived* from a body cavity or space" is withdrawn.

Applicants did not address this rejection in their Response of 7/5/07. Applicants have now addressed the rejection in the Response of 6/23/08 by amending Claim 1 to delete the term "derived" from Claim 1.

### *Double Patenting*

8. The provisional rejection of Claims 1-8, 11 and 12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 8, 19, 20 and 24 of copending Application No. 09/881,339 ("the '339" application; US 20030138860) in view of Robertson et al. (WO 99/58978; published November 18, 1999; cited in the PTO form-892 of 9/27/06) is withdrawn and moot.

Applicants state on p. 9 of the Response of 6/23/08 that the '339 application is abandoned and which the Examiner has confirmed to be correct.

## ***Rejections Maintained***

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The rejection of Claims 1-7 under 35 U.S.C. 102(b) as being anticipated by Hanash et al. (WO 00/26668; published 5/11/2000; cited in the IDS of 12/14/06) is maintained.

Applicants' allegations on pp. 7-8 of the Response have been considered nut are not found persuasive. Applicants allege the method requires "that the tumor marker proteins must be from a particular source, namely, the sample being tested for autoantibodies is contacted with ah immunoassay reagent wherein the immunoassay reagent comprises one or more tumor marker proteins prepared from a bodily fluid from a body cavity or space"; "Hanash fails to acknowledge the significance of using tumor marker proteins that are obtained from a body cavity or excretion of a cancer patient."

Response to Arguments

Hanash teaches immunoassay methods for detecting autoantibodies in samples against cancer or tumor-derived family of S100 proteins, where the S100 proteins are obtained from bodily fluids or a wide variety of protein mixtures containing S100 proteins, for example, at p. 6, lines 3-16:

> "sera and other biological fluids in which *secreted* proteins localize can be used to screen for increased levels of protein expression";

at p. 6, lines 17-20:

> "In a specific embodiment of invention, any member of the S100 protein family can be purified and utilized to screen a subject's serum for the presence of circulating autoantibodies to such protein antigens, by means of sensitive and rapid immunoadsorbent assays or by other procedures";

at p. 7, lines 3-4:

> "In accordance with the invention, measurement of levels of S100 proteins in serum or body fluids can be used for the earlv diagnosis of diseases such as cancer";

at p. 10, lines 10-21:

> "The present invention is demonstrated by way of example wherein elevated levels of an S 100 protein was detected in serum samples derived from cancer subjects. In particular, increased levels of SI00-A9 were detected in serum samples derived from colon and lung patients. In addition, S100-A7 and S100-A8 proteins were shown to be secreted by breast cancer cells, which provide the basis for diagnostic and prognostic assays for breast cancer. The detection and/or quantitative measurement of S 100 proteins in serum or other body fluids can be used in screening of subjects who are at risk for developing certain types of cancers or other proliferative disorders in which the S100 proteins are over expressed. In addition, qualitative differences in the pattern of occurrence in serum or biological fluids of different members of the S100 family of proteins can be used as a screening, diagnostic or prognostic indicator of cancer or cancer risk."

Hanash discloses four S100 proteins, specifically, S 100-AG, S 100-A7, S 100-A8 and S100-A9, and using these isolated proteins in immunoassays for detection of autoantibodies (Example 7). Hanash discloses using the methods for detection and quantitative measurement of S100 autoantibodies and in screening subjects for risk of cancer or other proliferative diseases (p. 6, lines 9-12) or for the early diagnosis of diseases such as cancer or monitoring of autoantibody levels to prognostically to stage the progression of the disease (p. 11, lines 1-4) or monitoring the efficacy of various therapeutic treatments for cancer (p. 4, line I p. 5, line 1).

One skilled in the art could readily envisage that the body fluids or biological fluids of Hanash could be obtained from a body cavity or space were any of the

disclosed cancers is present, was present or is associated within. Additionally, the claims are not limited to or nor do they define the meaning of "a body cavity or space" much less where the compartment is defined, for example, the circulatory system from where serum or plasma are assayed.

For example, Hanash teaches that breast cancer cells secrete S100-A7 and S100-A8 proteins (p. 10, line 13-15) thus secretion of the tumor marker into a compartment associated with the cancer such as a duct or cyst or hydrocoele would be inherent to the pathology of the disorder and obtaining the bodily fluid well within ordinary skill. Thus contrary to Applicant's assertion, in Example 7 Hanash shows that a tumor antigen can be *prepared* where the tumor proteins are separated and isolated by 2-D gel electrophoresis followed by membrane transfer and blotting with serum from a patient to determine the presence of autoantibodies. Finally, Applicants claims are not limited as how a tumor antigen protein is "prepared" or what constitutes a prepared antigen in order to patentably distinguish the claimed method from Hanash.

The rejection is maintained.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. The provisional rejection of Claims 1-8, 11, and 12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 8 and 9 of copending Application No. 10/417,633 ("the '633" application; US 20030232399) in view of Robertson et al. (WO 99/58978; published November 18, 1999; cited in the PTO form-892 of 9/27/06) is maintained.

Applicants state on p. 8 of the Response of 6/23/08 that they wish to defer filing a Terminal Disclaimer until allowable subject matter in the '633 application is established, and they have yet to do so.

## ***New Grounds for Rejection***

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### ***Enablement***

11. Claims 1-8, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting autoantibodies to circulating tumor marker proteins such as MUC1 in pleural effusions and serum from a patient with advanced breast cancer and to MUC16 (CA125) in serum from patients with ovarian masses and ascites from a patient with breast cancer comprising contacting a sample from a patient with MUC1 and/or MUC16 and determining the presence of absence of complexes of MUC1 and/or MUC16 bound to autoantibodies present in a sample, whereby the presence of said complexes is indicative of autoantibodies, does not reasonably provide enablement for the use of the method for detecting any cancer, detecting of early neoplastic or early carcinogenic change in asymptomatic patients. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many

factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Nature of the invention/ Skill in the art

The claims are drawn to a method of detecting autoantibodies in a subject by determining a complex formed between a tumor antigen and an autoantibody present in the body fluid and the use of said method in detecting cancer. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

Breadth of the Claims

Applicants broadly claim a method of detecting autoantibodies to tumor marker proteins prepared from a bodily fluid from a body cavity or space in which a tumor is or was present or associated with in one or more cancer patients comprising contacting a sample of bodily fluids from said subject with one or more tumor markers selected from and determining the presence or absence of said autoantibodies by complex formation with the tumor marker proteins in said bodily fluids, whereby the presence of said complexes is indicative of autoantibodies to the tumor markers (Claim 1). The claims

are further drawn to using the method described above, for detecting cancer (Claim 3), monitoring cancer progression or other neoplastic disease (Claim 4), detecting of early neoplastic or early carcinogenic change in asymptomatic patients (Claim 5), screening for a risk of developing cancer (Claim 6), monitoring the response of a patient to an anti-cancer treatment (Claim 7), and/or detecting a recurrent cancer in a subject already having undergone anti-cancer treatment (Claim 8). Claims 11 and 12 depend from Claims 1 and 3, respectively, and are drawn to the kind of bodily fluid from which the one or more tumor marker proteins are obtained.

Disclosure in the specification/ Working examples

The specification teaches that the instant invention relates to the use of a panel assay for the detection of autoantibodies which uses a panel of tumor marker-related antigens, wherein the panel is tailored to detect a particular cancer, or a cancer at a particular state of development (page 17, lines 13-18). With regards to the markers, the specification teaches that preferred markers include c-erbB2, MUC1, Myc, ras, p53, BRCA1, BRCA2, APC, CA125, PSA, CEA and CA19.9 (p. 17, line 25 to page 18, line 7). The specification further provides the following working examples utilizing MUC1 and MUC16 for the detection of autoantibodies of cancer patients:

Example 4 (working) serum from a patient with pleural effusions and serum from a patient with advanced breast cancer showed auto-reactive antibodies against MUC1 (Figure 4) compared to normal controls (Figure 5). Serum from patients with ovarian masses and ascites from a patient with breast cancer showed auto-reactive antibodies against MUC16 antigen (Figure 6).

Example 7 (working) MUC1 protein purified from pooled ascetic fluid and pleural effusion from patients with advanced breast cancer showed the protein to be as reactive to autoantibodies as the individually isolated MUC 1 protein (Figures 10 and 11).

Thus, while the specification clearly sets forth the presence of autoantibodies in a patient to MUC1 and MUC16 and using purified proteins for MUC1 and MUC16 in a panel assay for detecting cancer, the specification appears to be silent on the presence of autoantibodies to just any tumor antigen found in any bodily fluid from any body cavity or space and whether the presence of autoantibodies to these tumor antigens, alone or in combination, can be used for the detection of any cancer, monitoring any cancer progression or other neoplastic disease, detecting of early neoplastic or early carcinogenic change in asymptomatic patients, screening for a risk of developing any cancer, monitoring the response of a patient to any anti-cancer treatment, and/or detecting any recurrent cancer in a subject already having undergone any anti-cancer treatment. As such, if there is no correlation, then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of cancer diagnosis utilizing autoantibodies is extremely large given the unpredictability associated with only subsets of patients with a tumor developing a humoral-based autoantibody response to a

particular antigen and the lack of knowledge pertaining to the presence of autoantibodies to any caner-associated antigen being indicative of a particular cancer.

State of the prior art/ Unpredictability of the art

The state of the art at the time of filing was such that one of skill could recognize that the use of autoantibodies as serological markers for cancer diagnosis is an interesting concept because of the general absence of these autoantibodies in normal individuals and non-cancer conditions. For example, Stockert et al. (J. Exp. Med. 1998; 187: 1349-1354) teaches that there are a variety of known immunogenic human tumor antigens which generally fall into one of the following categories" (a) cancer-testis antigens; (b) antigens coded for by mutated genes, e.g., p53 and DCK4; (c) differentiation antigens, e.g., tyrosinase and Melan-A; (d) amplified gene products, e.g., Her2/neu and carbonic anhydrases; and viral antigens, e.g., retrovirus, HPV and EBV. In particular, Stockert et al. teach that a survey of sera from 234 cancer patients showed autoantibodies to NY-ESO-1 in 19 patients, to MAGE-1 in 3, to MAGE-3 in 2, and to SSX2 in 1; and no reactivity in sera from 70 normal individuals (page 1351, Table 2). Likewise, Zhang et al. (Cancer Epidemiology, Biomarkers & Prevention 2003; 12: 136-143) examined the reactivity's of several hundred sera from patients with six different types of cancer to a mini-array of seven selected tumor associated antigens (page 137, 1st column, 1st paragraph). Interestingly, Zhang et al. found that the frequency of antibodies to any individual antigen rarely exceeded 15 to 20%, but with the successive addition of antigens to the panel, there was a stepwise increase in the percentage of positive reactors to between 44 and 68% against a combined panel of seven antigens

(page 137, 1st column, 1st paragraph). More recently, Casiano et al. (Molecular & Cellular Proteomics 2006; 5: 1745-1759) lists over 40 candidate tumor associated antigens (TAAs) recognized by autoantibodies from prostate cancer patients. In particular, Casiano et al. teach that while tumor associated antigen (TAA) arrays provide a promising and powerful tool for enhancing cancer detecting and treatment; their utility in a clinical setting is currently in its infancy (page 1755, 2nd column, last paragraph). Thus, while these references cited above clearly show that autoimmunity can be associated with cancer in the form of the development of autoantibodies to autologous cellular antigens, the state of the prior art recognizes the unpredictability associated with cancer diagnosis utilizing autoantibodies because only subsets of patients with a tumor develop a humoral response to a particular antigen

The claims are not limited to any kind of tumor antigen panel or any cancer shown to have a correlation with tumor antigen expression and the detection of autoantibodies to the tumor antigen protein. However, if the ordinary artisan were to consider the art for any class of tumor antigens, using CYFR 21-1, annexin I and annexin II as examples, the state of the prior art at the time the invention was made recognizes that each represent diagnostic markers for a variety of cancerous conditions, as well as non-cancerous conditions. Both Steiber et al. (Cancer 1993; 72: 707-713) and Muraki et al. (Cancer 1996, 77: 1274-1277) found high levels of CYFR-1 in the sera of patients suffering from lung cancer. In addition to being a marker for lung cancer, Muraki et al. also teach that CYFRA 21-1 is useful as a tumor marker for breast carcinoma and gynecological malignant neoplasms, and further, has been reported to

be present at high levels in benign respiratory diseases, pulmonary tuberculosis, and intestinal pneumonia (page 1277, 1st column, last 2 full paragraphs). Similarly, both annexin I and annexin II have been shown to be expressed in a variety of tumors. For example, Brichory et al. (PNAS 2001: 98; 9824-9829) teach that both annexin I and annexin II are expressed in lung carcinomas (page 9827, Figure 4). Brichory et al. further teach that increased Annexin II expression is also associated with glioblastoma multiforme, pancreatic cancer and acute premyelocytic leukemia (page 9829, 2nd column, paragraph bridging column 1 and column 2). Thus, while the prior art recognizes that CYFRA 21-1, annexin I and annexin II represent diagnostic markers for a variety of cancerous conditions, as well as non-cancerous conditions, only autoantibodies to annexin I and annexin II, and not autoantibodies to CYFRA 21-1, have been taught in the prior art. For instance, Brichory et al. teaches that sera from 54 newly diagnosed patients with lung cancer, 60 patients with other cancers and 61 noncancer controls were analyzed for the presence of autoantibodies to annexin I and annexin II (page 9825, Table I). Specifically, Brichory teaches that sera from more than half of the patients with lung cancer exhibited autoantibodies to annexin I and/or annexin II, but only autoantibodies to Annexin II were found only in lung cancer patients in our series, whereas annexin I autoantibodies were observed in a few patients with other cancers. Thus, while the studies conducted by Brichory et al. clearly suggest a correlation between some patients with lung cancer and the presence of autoantibodies to annexin I and/or annexin II, the percentage of patients having such autoantibodies is

small compared to the total population and does not appear to suggest that the presence would be indicative of cancer (emphasis added).

A similar analogy can be made for the class of MUC1 or MUC16 cancer antigens and autoantibodies in detecting any disorder much less the correlation between the antigen expression, presence of autoantibody and the disease type. As an example, Treon et al. (Blood 96(6):3147-3153 (2000)) teach that there is an inverse relationship between soluble MUC1 expression in serum and the level of detectable IgM and IgG autoantibody in patients with multiple myeloma. The studies of Treon teach both IgM and IgG antibodies to MUC1 were detected in MM patients, however, the mean levels of both IgM- and IgG-circulating antibodies were lower than those detected in health humans (Table 2), soluble MUC1 were significantly higher in MM patients versus health patients, and mean soluble MUC1 levels were inversely related to mean anti-MUC1 antibody levels among MM patients and healthy patients (Table 1) (p. 3151, Col. 1, ¶1). Thus the value in detecting autoantibodies at least against MUC1 tumor antigen in MM patients would not have been correlative with disease presence nor could detecting MUC1 antibodies in any cancer patient as instantly claimed provide a basis for detection of any cancer, monitoring any cancer progression or other neoplastic disease, detecting of early neoplastic or early carcinogenic change in asymptomatic patients, screening for a risk of developing any cancer, monitoring the response of a patient to any anti-cancer treatment, and/or detecting any recurrent cancer in a subject already having undergone any anti-cancer treatment.

As to correlating disease specificity with the detection MUC 16 (CA125), Szekanecz et al. (Ann. NY Acad Sci 1108:359-371 (2007) Abstract) teaches that the tumor antigen, CA125 (MUC16) is increased (10.8%) in patients serum with rheumatoid arthritis measured by immunoassay compared to controls (7.1%). Thus not only is MUC 16 expressed in serum of normal subjects but to a greater extent in a cancer-unrelated disorder. These studies establish that there is no strict correlation between MUC 16 tumor markers in a body cavity from a subject and the correlation to cancer. Still further, it us even less tenable how the detection of autoantibodies would be a diagnostic indicia for cancer under these circumstance.

In the instant case, if autoantibodies to MUC1 and/or MUC16 are to be considered as a surrogate for a disease state, a specific disease state must be identified in some way with the molecule. There must be some pattern that would allow the autoantibodies to MUC1 and/or MUC16 to be used in a consistent, specific, predictable and verifiable diagnostic manner for a particular disease. For example, as noted above, those of skill in the art recognize that the antigens MUC1 and MUC16 have been individually taught to be variable insofar as their correlative accuracy in diagnosing any kind of cancer. In the absence of any correlation between the instant claimed autoantibodies with any known disease or disorder, any information obtained from various expression profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself. Therefore, absent evidence of the autoantibodies presence including the correlation to a diseased state, one of skill in the art would not be able to predictably use the antigen in any diagnostic setting without

undue experimentation. Autoantibody assays against a panel of antigens could be used as an aid to art-recognized, standardarized cancer detection/monitoring procedures but as a stand alone diagnostic, the claimed method is not enabled.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlating success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

## ***Conclusion***

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Temporary Partial Signatory Authority